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(21) International Application Number: PCT/US96/04553 (22) International Filing Date: 3 April 1996 (03.04.96) (30) Priority Data: 08/415,488 3 April 1995 (03.04.95) US (71) Applicant: BONE CARE INTERNATIONAL, INC. [US/US]; 313 West Beltline Highway, Madison, WI 53713 (US). (72) Inventors: KNUTSON, Joyce, C.; 24 North Prospect Avenue, Madison, WI 53705 (US). MAZESS, Richard, B.; 2526 Gregory Street, Madison, WI 53711 (US). BISHOP, Charles, W.; 5 LaPointe Terrace, Madison, WI 53719 (US). (74) Agents: WELCH, Teresa, J. et al.; Stroud, Stroud, Willink, Thompson & Howard, Suite 300, 25 West Main Street, P.O. Box 2236, Madison, WI 53701-2236 (US).		(81) Designated States: AU, BR, CA, CN, FI, HU, JP, KR, MX, NO, NZ, PL, SG, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: USE OF VITAMIN D ₂ OR VITAMIN D ₄ -DERIVATIVES FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF SECONDARY HYPERPARATHYROIDISM (57) Abstract A method for preventing loss of bone mass or bone mineral content in a human being suffering from secondary hyperparathyroidism by administering a sufficient amount of 1 α -OH vitamin D ₂ , 1 α ,24(S)-(OH) ₂ vitamin D ₂ , 1 α -OH vitamin D ₄ or 1 α ,24(R)-(OH) ₂ vitamin D ₄ .		

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USE OF VITAMIN D2 OR VITAMIN D4-DERIVATIVES FOR THE MANUFACTURE OF A
MEDICAMENT FOR THE TREATMENT OF SECONDARY HYPERPARATHYROIDISM

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This application is a continuation-in-part of U.S. Patent Application No. 08/119,895, which is a continuation of U.S. Patent Application No. 07/569,412, now U.S. Patent 5,104,864.

TECHNICAL FIELD

10 This invention relates generally to methods for treating and preventing metabolic bone disorders characterized by loss of bone mass or by disproportionately low bone mineral content. More specifically, this invention relates to a method for treating or preventing hyperparathyroidism secondary to end-stage renal disease, one of the concomitant results of which is the loss of
15 bone mass or decreased mineral content (i.e., renal osteodystrophy).

BACKGROUND OF THE INVENTION

Numerous metabolic bone disorders are known which are characterized by loss of bone mass or bone mineral. These disorders include postmenopausal osteoporosis, senile osteoporosis, corticosteroid-induced osteopenia,
20 anticonvulsant osteomalacia and renal osteodystrophy. Of these disorders, renal osteodystrophy is encountered in end-stage renal disease patients undergoing chronic dialysis.

As a group, these bone depletive disorders are a major and growing public health problem in the United States. Together, they cause more than 1 million
25 bone fractures per year, primarily of the spine, hip, and distal forearm, and result in an annual cost above \$10 billion to the American society. Unfortunately, the incidence of these bone disorders will rise significantly as the mean age of the U.S. population continues to increase.

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observed on bone. [See G. F. Jensen et al., *Clin. Endocrinol.* 16, 515-524 (1982); C. Christiansen et al., *Eur. J. Clin. Invest.* 11, 305-309 (1981)]. Doses of 2 $\mu\text{g/day}$ of $1\alpha\text{-OH vitamin D}_3$ were found to have efficacy in increasing bone mass in patients exhibiting senile osteoporosis [O. H. Sorensen et al., *Clin. Endocrinol.* 7, 169S-175S (1977)]. Data from clinical studies in Japan, a population that has low calcium intake, indicate that efficacy is found with $1\alpha\text{-OH vitamin D}_3$ when administered at 1 $\mu\text{g/day}$ [M. Shiraki et al., *Endocrinol. Japan.* 32:305-315 (1985); H. Orimo et al., *Bone and Mineral* 3, 47-52 (1987)]. However, at 2 $\mu\text{g/day}$, toxicity with $1\alpha\text{-OH vitamin D}_3$ occurs in approximately 67 percent of the patients, and at 1 $\mu\text{g/day}$ this percentage is approximately 20 percent.

Thus, the prior art teaches that due to their toxicity, 1-hydroxylated vitamin D compounds can only be administered at dosages that are, at best, modestly beneficial in preventing or treating loss of bone or bone mineral content. Indeed, Aloia recommends that alternative routes of administration be sought which might avoid the toxicity problems and allow higher dosage levels to be achieved. [J. Aloia et al., *Amer. J. Med.* 84:401-408 (1988)].

Despite reported toxicities of $1\alpha\text{-OH vitamin D}_3$ and $1\alpha,25\text{-(OH)}_2\text{ vitamin D}_3$, these two compounds remain the drugs of choice for many bone depletive disease treatments. For example, in end stage renal disease, these two drugs remain the only approved forms of $1\alpha\text{-hydroxylated vitamin D}$ for treating or preventing secondary hyperparathyroidism, although both drugs are not currently approved in all major pharmaceutical markets.

At present, in the United States, end stage renal disease afflicts approximately 200,000 individuals. In this disease, there is a progressive loss of cells of the proximal nephrons, the primary site for the synthesis of the vitamin D hormones (collectively " $1\alpha,25\text{-(OH)}_2\text{D}$ ") from 25-hydroxyvitamin D_3 and 25-hydroxyvitamin D_2 . In addition, the loss of functioning nephrons leads to retention of excess phosphorus which reduces the activity of the renal 25-hydroxyvitamin $\text{D-}1\alpha\text{-hydroxylase}$, the enzyme which catalyzes the reaction to produce the D hormones. These two events account for the low serum levels

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To reduce the incidence of toxic side effects with $1\alpha,25-(\text{OH})_2\text{D}_3$ or $1\alpha\text{-OH-D}_3$, a low calcium dialysate with an ionized calcium concentration of 1.25 mM has been developed. However, it has been found that use of the low calcium dialysate has lead to higher serum PTH and phosphorus levels in patients
5 who do not receive increased doses of oral calcium supplements and phosphate binders. When the dosages of calcium supplements and phosphate binders are increased, serum levels of phosphorus become controlled, but the incidence of hypercalcemia rises markedly. Thus, there are many problems associated with the use of current vitamin D therapies for secondary hyperparathyroidism.

10 Notwithstanding these known problems with use of the hormonally active vitamin D_3 for secondary hyperparathyroidism, the art has not adequately responded to date with the introduction of other vitamin compounds, derivatives or analogs that possess less inherent toxicity.

SUMMARY OF THE INVENTION

15 The present invention provides a method for treating or preventing hyperparathyroidism secondary to end stage renal disease by lowering (or maintaining low) serum parathyroid hormone levels in a patient suffering from the disease. The method at the same time ameliorates or prevents the renal osteodystrophy which can develop in such patients.

20 The foregoing, and other advantages of the present invention, are realized in one aspect thereof in a method for lowering serum (or plasma) PTH in patients suffering from hyperparathyroidism secondary to end stage renal disease, comprising: administering to these patients an effective amount of a vitamin D analog of formula (I), as described hereinbelow, to lower the serum PTH level.

25 The analog of formula (I) is any active vitamin D compound which has potent biological activity but low calcemic activity relative to the active forms of vitamin D_3 . Preferably such compounds are $1\alpha\text{-OH-vitamin D}_2$; $1\alpha,24(\text{S})-(\text{OH})_2\text{-vitamin D}_2$; $1\alpha\text{-OH-vitamin D}_4$; or $1\alpha,24(\text{R})-(\text{OH})_2\text{-vitamin D}_4$. The analog of formula (I) is administered in a dosage amount of 1 to about 100 $\mu\text{g/week}$. As
30 used herein, the term "vitamin D analog" is meant to refer to compounds having

DETAILED DESCRIPTION

The present invention relates broadly to bone depletive disorders. However, the method of the present invention is most particularly adapted for use in ameliorating or preventing hyperparathyroidism secondary to end stage renal disease. The method also ameliorates or prevents the concomitant renal osteodystrophy of these patients with this disease. Accordingly, the present invention will now be described in detail with respect to such endeavors; however, those skilled in the art will appreciate that such a description of the invention is meant to be exemplary only and should not be viewed as limitative on the full scope thereof.

More specifically, the present invention relates to therapeutic methods for lowering the excessively high blood levels of parathyroid hormone (PTH) which are secondary to end stage renal disease. The method in accordance with the present invention has significantly less resultant hypercalcemia and hyperphosphatemia, especially in patients who use oral calcium phosphate binders to control serum phosphorus levels. These attributes are achieved through a novel treatment of a patient suffering from secondary hyperparathyroidism with a vitamin D analog of formula (I) as described hereinbelow.

In accordance with the invention, it has been found that when the analogs of formula (I) are administered to end stage renal disease patients with elevated serum parathyroid hormone, PTH concentration is lowered with significantly less hypercalcemia and hyperphosphatemia than is observed after the same amount of activated vitamin D administered in previously known formulations. Thus, the compounds of formula (I) have an improved therapeutic index relative to vitamin D₃ analogs.

forms of the two vitamins to be equivalent despite lack of confirmation from a single human study. (It is also interestingly noted that vitamin D₄ is described in *The Merck Index* (Merck Index, 11th ed. (1989) p. 9932) as having doubtful biological activity.)

5 In parent application, Serial No. 08/119,895 and its parent application, now U.S. Patent 5,104,864, it has been shown that 1 α -OH-vitamin D₂ has the same biopotency as 1 α -OH-vitamin D₃ and 1 α ,25-(OH)₂-vitamin D₃ but is much less toxic. Even dosages up to 10 μ g/day of 1 α -OH-vitamin D₂ in women with postmenopausal osteoporosis (in both open label and double blind testing)
10 exhibited only mild hypercalciuria (> 300 mg/24 hrs), and marked hypercalcemia (> 11.0 mg/dL) solely due to 1 α -OH-vitamin D₂ was not evident. Additionally, the compound did not adversely affect kidney function, as determined by creatinine clearance and BUN; nor did it increase urinary excretion of hydroxyproline, indicating the absence of any stimulatory effect on bone
15 resorption. Administration of 1 α -OH-vitamin D₂ to healthy adult males in dosages up to 8 μ g/day showed no hypercalcemia or other adverse effects.

 The analogs of formula (I) are useful as active compounds in pharmaceutical compositions. The pharmacologically active analogs of this invention can be processed in accordance with conventional methods of pharmacy
20 to produce pharmaceutical agents for administration to patients, e.g., in admixtures with conventional excipients such as pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral (e.g., oral) or topical application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include but are not limited to water,
25 salt (buffer) solutions, alcohols, gum arabic, mineral and vegetable oils, benzyl alcohols, polyethylene glycols, gelatine, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy methylcellulose, polyvinyl pyrrolidone, etc. The pharmaceutical
30 preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for

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particular compositions formulated, the mode of application, and the particular
situs being treated. Dosages can be determined using conventional
considerations, e.g., by customary comparison of the differential activities of the
subject compounds and of a known agent, e.g. by means of an appropriate
5 conventional pharmacological protocol.

The specific doses for each particular patient depend on a wide variety of
factors, for example, on the efficacy of the specific compound employed, on the
age, body weight, general state of health, sex, on the diet, on the timing and
mode of administration, on the rate of excretion, and on medicaments used in
10 combination and the severity of the particular disorder to which the therapy is
applied.

It is possible, if desired, to produce the metabolites of certain ones of the
analogs of formula (I), in particular by nonchemical means. For this purpose,
it is possible to convert them into a suitable form for administration together with
15 at least one vehicle or auxiliary and, where appropriate, combined with one or
more other active compounds.

The dosage forms may also contain adjuvants, such as preserving or
stabilizing adjuvants. They may also contain other therapeutically valuable
substances or may contain more than one of the compounds specified herein and
20 in the claims in admixture.

Bulk quantities of the vitamin D analogs for the practice of this invention
can be readily obtained in accordance with the processes of U.S. Patents
Nos. 3,907,843; 4,195,027; 4,202,829; 4,234,495; 4,260,549; 4,555,364; and
4,554,106 and U.S. Patent Application Serial Nos. 08/275,641 and 08/296,084.

25 As described hereinbefore, the analogs of formula (I) are preferably
administered to the human patients in oral dosage formulation. As an analog in
accordance with the present invention is released from the oral dosage
formulation, it is absorbed from the intestine into the blood.

The present invention is further explained by the following examples
30 which should not be construed by way of limiting the scope of the present
invention.

5 A positive effect of 1α -OH-vitamin D₂ on calcium homeostasis was evident from dose-related increases observed in 24-hour urinary calcium levels, confirming that the compound increases intestinal calcium absorption, and from dose-related increases in serum osteocalcin, suggesting that the compound directly stimulates bone formation.

Example 2: Study Demonstrating Safety and Efficacy for Human Osteoporosis

10 The safety and efficacy of 1α -OH-vitamin D₂ as an oral treatment for osteoporosis was confirmed in a study involving 60 postmenopausal osteoporotic outpatients. The selected subjects had ages between 60 and 70 years, and exhibited L2-L3 vertebral BMD between 0.7 and 1.05 g/cm², as determined by dual-energy x-ray absorptiometry (DEXA). Exclusion criteria encompassed significant medical disorders and recent use of medications known to affect bone or calcium metabolism.

15 On admission to the study, each subject was assigned at random to one of two treatment groups; one group received up to a 104-week course of therapy with 1α -OH-vitamin D₂; the other received only placebo therapy. All subjects received instruction on selecting a daily diet containing 700-900 mg of calcium and were advised to adhere to this diet over the course of the study. Compliance
20 to the diet was verified at regular intervals by 24-hour food records and by interviews with each subject.

During the treatment period, subjects from one group orally self-administered 1α -OH-vitamin D₂ at an initial dosage of 1.0 µg/day for one week, and increased the dosage to 2.0, 3.0, 4.0 µg/day in each of the following weeks,
25 to a maximum dosage of 5.0 µg/day. The dosage for any given subject was increased in this way until the rate of urinary calcium excretion was elevated to approximately 275-300 mg/24 hours, at which point the subject held the dosage constant at the highest level attained. Subjects from the second group self-administered a matching placebo medication every day, titrating the apparent

Episodes of Hypercalcemia/Hypercalciuria: Marked hypercalcemia (> 10.8 mg/dL) occurred in one subject in association with an intercurrent illness. The prescribed dosage of 1α -OH-vitamin D₂ at the time of this episode was 5.0 µg/day. Moderate hypercalcemia (10.4-10.8 mg/dL) occurred in two subjects over the course of the study at prescribed dosages of 5.0 µg/day. Mild hypercalcemia (10.2-10.4 mg/dL) occurred in four subjects in the first year, and in two subjects in the second year. Hypercalciuria was observed occasionally over the two-year study in 17 subjects treated with 1α -OH-vitamin D₂.

Serum Calcium/Ionized Calcium: Mean serum calcium was approximately 0.1 to 0.2 mg/dL higher in subjects treated with 1α -OH-vitamin D₂ than in subjects treated with placebo. This difference was significant ($P < 0.05$) only during the second year of treatment. Mean serum ionized calcium was approximately 0.05 to 0.10 mg/dL higher in subjects treated with 1α -OH-vitamin D₂.

Urine Calcium: Mean urine calcium increased during the initial titration period in a dose-response fashion. After titration, mean urine calcium was 50 to 130% higher ($P < 0.001$) with 1α -OH-vitamin D₂ treatment than with placebo treatment.

Kidney Function: No significant changes were observed with long-term 1α -OH-vitamin D₂ treatment in BUN, serum creatinine or creatinine clearance. KUB x-rays revealed no abnormalities in either treatment group throughout the course of the study.

Bone: Bone mineral density (BMD) in the L2-L4 vertebrae progressively increased with 1α -OH-vitamin D₂ treatment and decreased with placebo treatment over the two-year study. The difference in spinal BMD between the treatment groups became statistically significant ($P < 0.05$) after 24 months of treatment. Similar changes were observed in femoral neck BMD with statistically significant differences observed after 18 months ($P < 0.001$) and 24 months ($P < 0.05$) of treatment.

Calcium Uptake: Intestinal absorption of orally administered ⁴⁵Ca increased by 40% ($P < 0.001$) after 52 weeks of 1α -OH-vitamin D₂ therapy, and

1α -OH-vitamin D₂ is safe and effective in the treatment of postmenopausal or senile osteoporosis.

Example 3: Open Label Study in End Stage Renal Disease Patients Exhibiting Secondary Hyperparathyroidism

5 Five end stage renal disease patients were enrolled in an open label study. The selected patients had ages between 36 and 72 years and had been on hemodialysis for at least 4 months prior to enrollment. The patients each had an average serum phosphorus in the range of 3.0 to less than or equal to 6.9 mg/dL during the two months prior to enrollment (often controlled by oral calcium phosphate binders), and had a history of elevated serum PTH values of greater
10 than 400 pg/mL when not receiving $1\alpha,25$ -(OH)₂-vitamin D₃ therapy.

 Each patient had been receiving $1\alpha,25$ -(OH)₂ vitamin D₃ prior to enrollment, and discontinued the $1\alpha,25$ -(OH)₂ vitamin D₃ therapy for eight weeks prior to receiving 1α -OH-vitamin D₂. After 8 weeks, the patients received
15 treatment of 1α -OH-vitamin D₂ at a dosage of 4 µg/day for 6 weeks. Throughout the eight-week washout period and the treatment period, patients were monitored weekly or biweekly for serum intact PTH level and weekly for excessive elevation in serum levels of calcium and phosphorus.

 Throughout the washout period and treatment period, patients underwent
20 routine hemodialysis (3 times per week) using a 1.25 mM calcium dialysate. They also ingested significant amounts of calcium phosphate binders (1-10g elemental Ca) to keep serum phosphorus levels below 6.9 mg/dL.

 Baseline serum PTH was 480 ± 21 ; SCa (mg/dl), 9.8 ± 0.3 and serum phosphorus (mg/dl), 5.1 ± 0.2 . In three patients, serum PTH decreased by 68%,
25 74% and 87% after two weeks. In the other two patients, serum PTH declined by 33% in one and 3% in the other after four weeks. Overall, serum PTH decreased by $49\pm17\%$ and $33\pm9\%$ after two and four weeks of 1α -OH-vitamin D₂, respectively, ($p<0.05$). Serum calcium was 10.2 ± 0.4 ($p<0.05$) and 9.8 ± 0.2 (NS) and serum phosphorus was 5.4 ± 0.5 and 5.5 ± 0.8
30 at two and four weeks, respectively (NS). A rise in serum PTH from the second

Analysis of the clinical data show that 1α -OH-vitamin D₂ significantly increases serum osteocalcin levels and intestinal calcium absorption, as determined by direct measurement using a double-isotope technique. Patients treated with this compound show normalized serum calcium levels, stable values
5 for total body calcium, and stable radial and spinal bone densities relative to baseline values. In contrast, patients treated with placebo show frequent hypocalcemia, significant reductions in total body calcium and radial and spinal bone density. An insignificant incidence of hypercalcemia is observed in the treated group.

10 **Example 5: Double-blind Study in End Stage Renal Disease (ESRD)
Patients Exhibiting Secondary Hyperparathyroidism**

Up to 120 ESRD (End Stage Renal Disease) patients undergoing chronic hemodialysis are studied in a multicenter, double-blind, placebo-controlled study based in two major U.S. metropolitan areas. The selected patients reside in two
15 major metropolitan areas within the continental U.S., have ages between 20 and 75 years and have a history of secondary hyperparathyroidism. They have been on hemodialysis for at least four months, have a normal (or near normal) serum albumin, and have controlled serum phosphorus (often by using oral calcium phosphate binders).

20 On admission to the study, each patient is assigned at random to one of two treatment groups. One of these groups receives two consecutive 12-week courses of therapy with 1α -OH-vitamin D₂; the other receives a 12-week course of therapy with 1α -OH-vitamin D₂ followed, without interruption, by a 12-week course of placebo therapy. Each patient discontinues any $1\alpha,25$ -OH₂-vitamin D₃
25 therapy for eight weeks prior to initiating 1α -OH-vitamin D₂ therapy (4 μ g/day). Throughout this eight-week washout (or control) period and the two subsequent 12-week treatment periods, patients are monitored weekly for serum calcium and phosphorus. Serum intact PTH is monitored weekly or biweekly, and bone-specific serum markers, serum vitamin D metabolites, serum albumin, blood
30 chemistries, hemoglobin and hematocrit are monitored at selected intervals.

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being substantially less toxic than $1\alpha,25-(\text{OH})_2$ -vitamin D_3 and 1α -OH-vitamin D_3 . It is to be understood that although the foregoing examples detail the use of 1α -OH-vitamin D_2 , other compounds within the scope of the claims may be readily utilized in the treatment of this invention with essentially
5 equivalent results. For example, $1\alpha,24(\text{S})-(\text{OH})_2$ -vitamin D_2 shows activity equivalent to $1\alpha,24(\text{R})-(\text{OH})_2$ -vitamin D_3 and is also significantly less toxic than its vitamin D_3 counterpart. Also included within the scope of the claims would be administration of effective dosages of the analog of formula (I) in conjunction
10 with administration of other hormones or other agents which have been shown to stimulate bone formation in subjects experiencing or tending toward loss of bone mass or bone mineral content.

Such hormones or other agents may include conjugated estrogens or their equivalents, calcitonin, biphosphonates, calcium supplements, cobalamin, pertussis toxin and boron. Possible dose ranges for these co-administered agents
15 are provided in Table 1.

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encompassed by the present invention and that the scope of the present invention be limited solely by the broadest interpretation that lawfully can be accorded the appended claims.

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5. The method of claim 1 wherein said analog is administered in combination with at least one agent characterized by said agent's ability to reduce loss of bone mass, or bone mineral content in patients.

6. The method of claim 5 wherein said agent includes other vitamin D compounds, conjugated estrogens, sodium fluorides, biphosphonates, cobalamin, pertussin toxin or boron.

7. The method of claim 1, wherein said administration of said analog is parenteral.

8. The method of claim 7 wherein said administration is by subcutaneous, intramuscular, or intravenous injection, nasopharyngeal or mucosal absorption, or transdermal absorption.

9. The method of claim 1 wherein said administration of said analog is nonparenteral.

10. A pharmaceutical composition having serum parathyroid hormone lowering activity, comprising, in unit dosage form, an effective amount of a vitamin D analog which is 1α -OH-vitamin D_2 ; $1\alpha,24(S)$ -(OH) $_2$ -vitamin D_2 ; 1α -OH-vitamin D_4 ; or $1\alpha,24(R)$ -(OH) $_2$ -vitamin D_4 ; and a pharmaceutically acceptable excipient.

11. The composition of claim 10, wherein said amount is 0.25 to 5.0 μ g.

12. A pharmaceutical composition as claimed in claim 10 which further comprises, in combination, at least one agent characterized by said agent's ability to reduce loss of bone mass or bone mineral content in mammals experiencing or tending toward said loss of bone mass or bone mineral content.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 96/04553

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/59

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>BIOCHEM. J., vol. 310, no. 1, 15 August 1995, pages 233-241, XP002010503 STRUGNELL S. ET AL.: "1alpha,24(S)-dihydroxyvitamin D2: a biologically active product of 1alpha-hydroxyvitamin D2 made in the human hepatoma, Hep3B" see abstract see page 233, left-hand column, line 14 - line 20 see page 234, left-hand column, last paragraph see page 240, right-hand column, last paragraph</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1-16

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Int. Patent Application No.

PCT/US 96/04553

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 16711 (LUNAR CO) 4 August 1994 see page 2, line 22 - page 3, line 15 see page 6, line 21 - line 30 ---	10-14
X	US,A,4 833 125 (NEER ET AL.) 23 May 1989 see column 3, line 55 - line 68 see column 6; table 1 see column 7, line 16 - column 8, line 12 see claims 1-8 ---	10-14
X	US,A,4 698 328 (NEER ET AL.) 6 October 1987 see column 3, line 55 - line 67 see column 5, line 18 - line 58 see column 6; table 1 see column 7, line 1 - line 43 ---	10-14
X	EP,A,0 503 630 (KURARAY CO., LTD.) 16 September 1992 see page 2, line 55 - page 3, line 1 ---	1,2
X	EP,A,0 562 497 (NISSHIN FLOUR MILLING CO. LTD.) 29 September 1993 see page 2, line 51 - page 3, line 15 see page 7, line 48 - page 8, line 27 see page 11; example 2 see claims 1,3-5 -----	10-14

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